Dilution of Efficacy in Microbicide Trials

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MTN
microbicide trials network

Overview

- Definition of efficacy dilution
- Sources of dilution in microbicide trials
- Overall impact of dilution
- A case in point: The Carraguard Trial
- Conclusions

What is ‘dilution of efficacy’

- First, let’s talk about ‘efficacy’

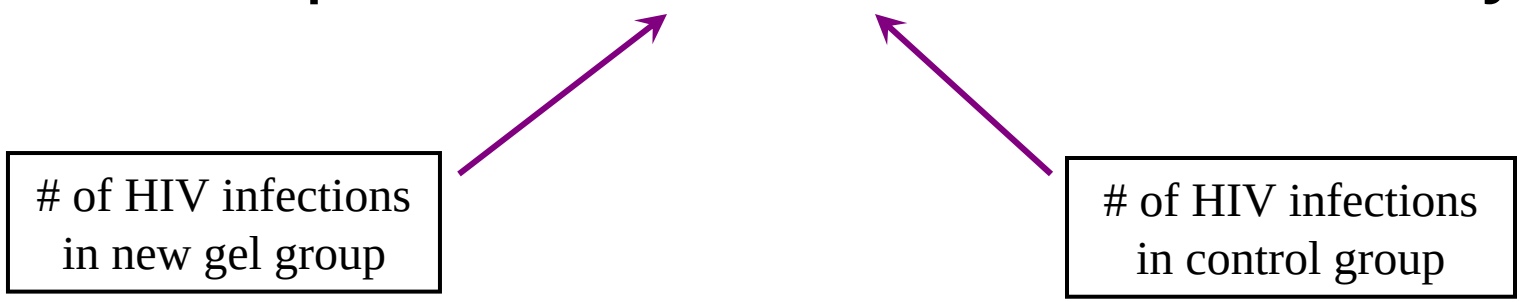
  How do we define the ‘efficacy’ of a microbicide gel?

- Efficacy is defined in terms of a comparator or control group (eg a group using a placebo gel or no gel)

A very simple formula for computing the efficacy

$$1 - \frac{[\text{\# of HIV infections in new gel group}]}{[\text{\# of HIV infections in the control group}]}$$

Example, 1 - 50/100 = 50% efficacy



A very simple formula for computing the efficacy

- HPTN 035 Pro2000 vs No gel:

1 – 36/53 = 32.1% [32.8%]

- Latest Thailand HIV Vaccine Trial Results:

1 – 51/74 = 31.1% [31.2%]

- MDP-301 Results:

1 – X/Y = Z%

What is ‘dilution of efficacy’

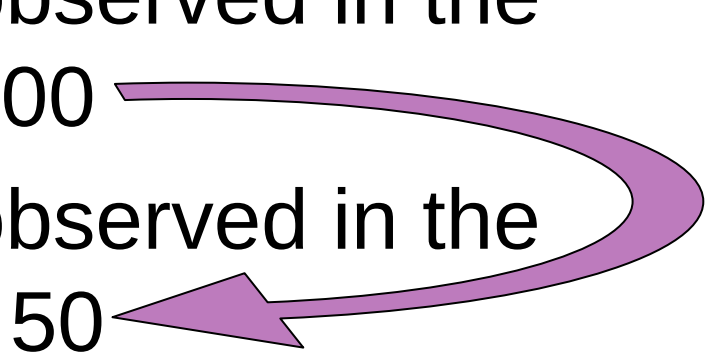
Say that the ‘true efficacy’ of new gel is 50%

- The ‘true efficacy’ will never be known … we can only get an estimate of it.

Conduct a randomized clinical trial (RCT):

# of HIV infections observed in the control group: 100

# of HIV infections observed in the microbicide group: 50



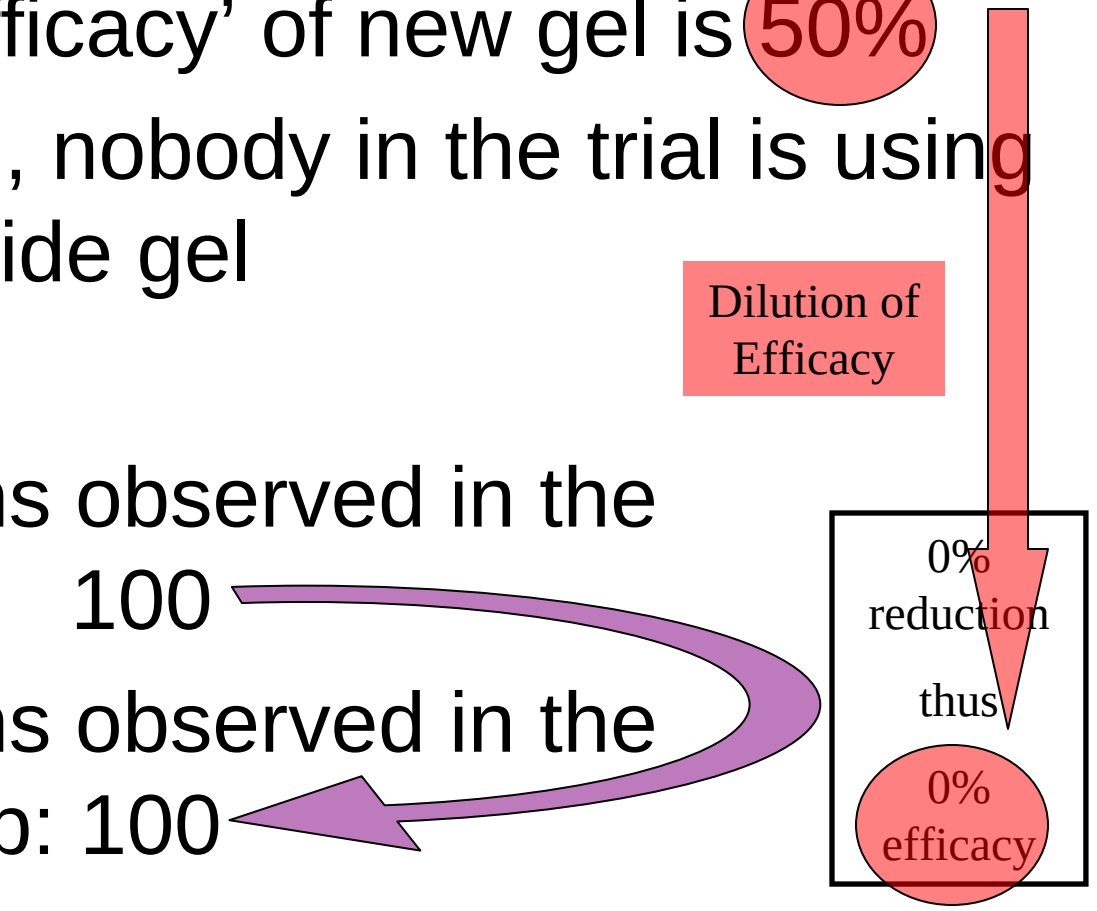
Example of ‘dilution of efficacy’

Say that the ‘true efficacy’ of new gel is 50%

- For some reason, nobody in the trial is using the new microbicide gel

# of HIV infections observed in the control group: 100

# of HIV infections observed in the microbicide group: 100



But we do not know the true efficacy

Say that the ‘true efficacy’ of new gel is ??%

Dilution of efficacy

?? or ??

New gel does not work

# of HIV infections observed in the control group: 100

# of HIV infections observed in the microbicide group: 100

0% reduction

thus

0% efficacy

But we do not know the true efficacy

Say that the ‘true efficacy’ of new gel is ??%

Partial Dilution of efficacy

?? or ??

New gel has low efficacy

# of HIV infections observed in the control group: 100

# of HIV infections observed in the microbicide group: 80

20% reduction

thus

20% efficacy

True efficacy > Observed Effectiveness

Say that the ‘true efficacy’ of new gel is ??%

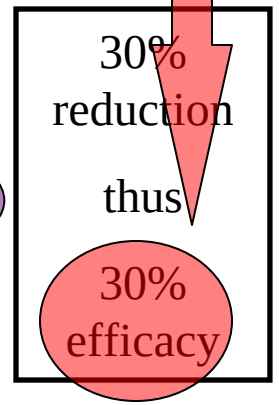
New gel has moderate efficacy

but

True efficacy likely to be higher than 30% in presence of partial dilution

# of HIV infections observed in the control group: 100

# of HIV infections observed in the microbicide group: 70



Sources of dilution in microbicide trials

- Adherence / Product Use
  - Need to use the gel in order to benefit from its potential protective effect to prevent HIV acquisition

In HPTN 035,

Gel was used in about 8 out of 10 vaginal acts … ~ 80% adherence

Sources of dilution in microbicide trials

- Time Off-Product / Product Hold
  - Temporary or permanent product withdrawal:
    - Due to pregnancy
    - Or due to other emerging conditions (eg AEs)

In HPTN 035,

3940 person-years in the 3 gel arms

240 person-years with product hold (6.1%)

Sources of dilution in microbicide trials

- Anal Intercourse as a source of HIV infection
  - Gel can only protect vaginal acts
  - If many of the HIV infections in a trial are acquired from unprotected anal intercourse then this will dilute the efficacy of the gel

In HPTN 035,

Of the 194 HIV infections, we have absolutely no idea how many could have been acquired from unprotected anal intercourse

So, no data … how about an estimate

- A model for the cumulative risk (*CR*) over 3 months of HIV infection:

$CR = 1 - ((1-p)^{n*f} * (1- (RR*p))^{n*(1-f)})$ where

p per act male-to-female transmission probability
n # of unprotected sex acts in 3 mos
f fraction of sex acts that are vaginal
RR increase in risk for AI compared to vaginal intercourse

Using the above model, we can simulate a trial like HPTN 035 and get an estimate of the number of HIV infections that could have been acquired from unprotected AI:

20% ~ 40 out of the 194 HIV infections

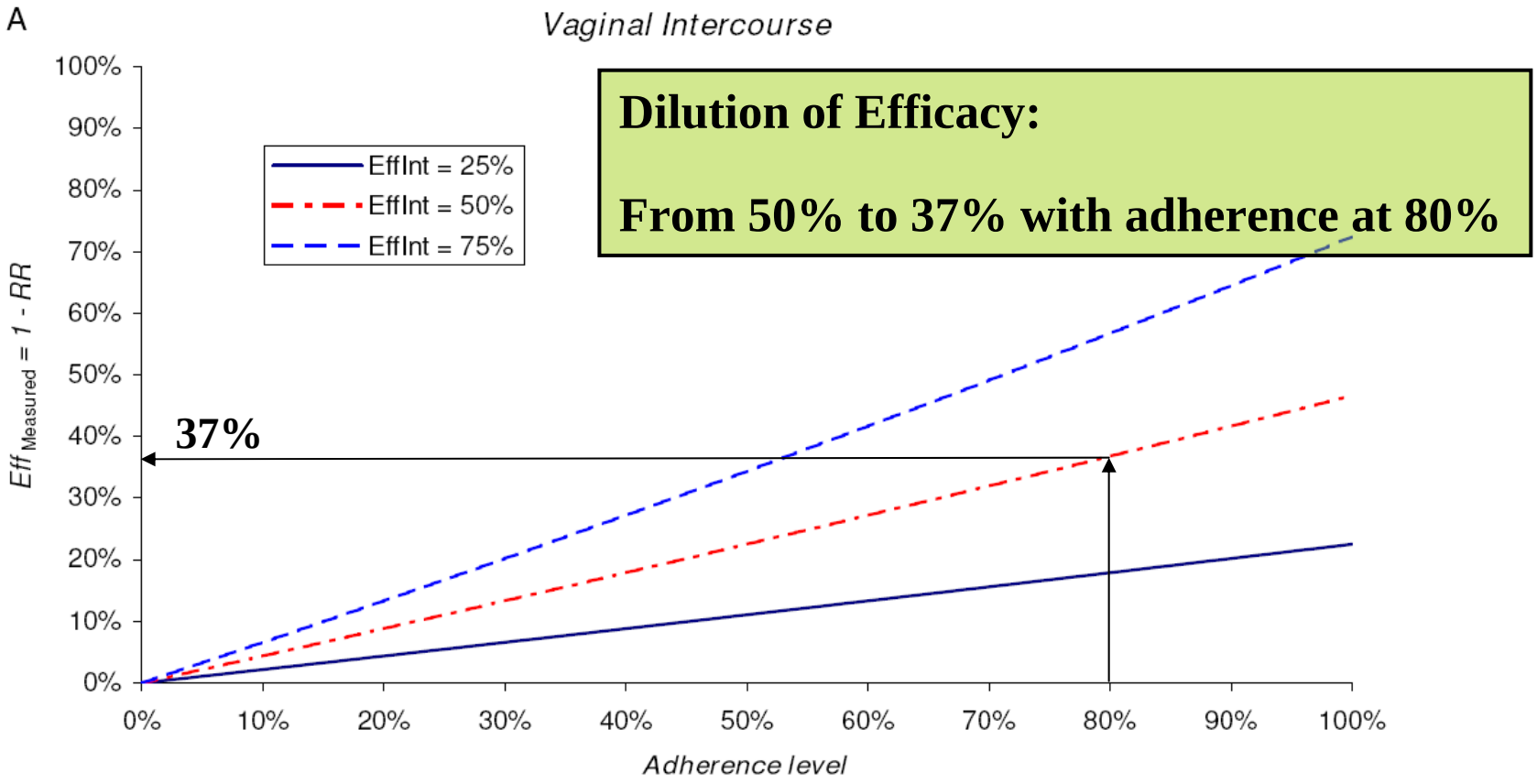
Sources of dilution in microbicide trials

- Placebo Physical Barrier / Lubrication Effect
  - If the placebo gel has a protective effect, this will dilute the efficacy of the new gel
  - 5 different placebo gels have been used in microbicide trials

In HPTN 035,

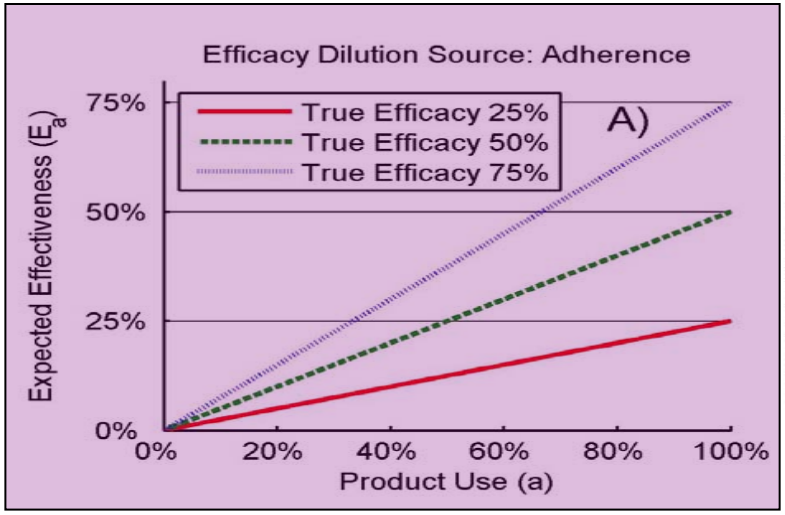
An efficacy of 3% was observed for the universal placebo gel [using the ‘no gel’ group as the control group]

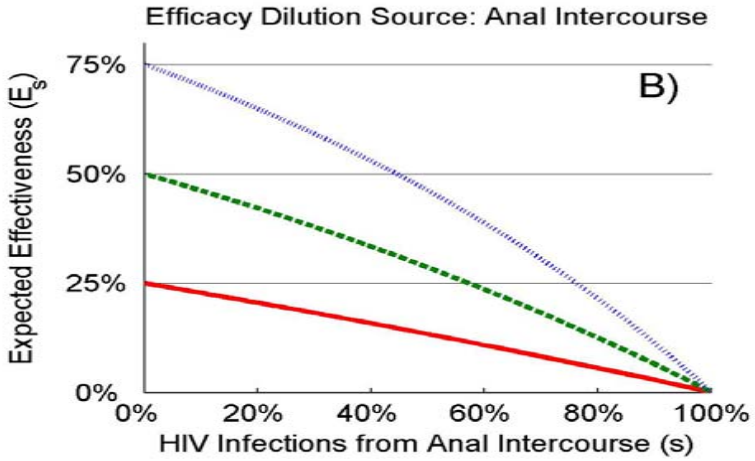
Dilution of Efficacy: Adherence

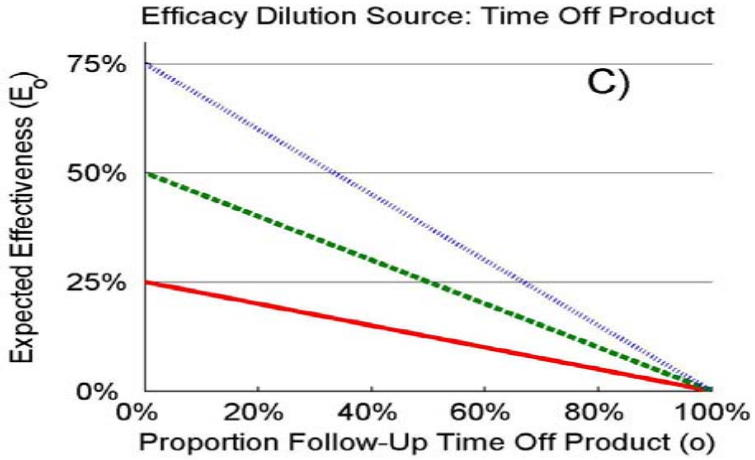


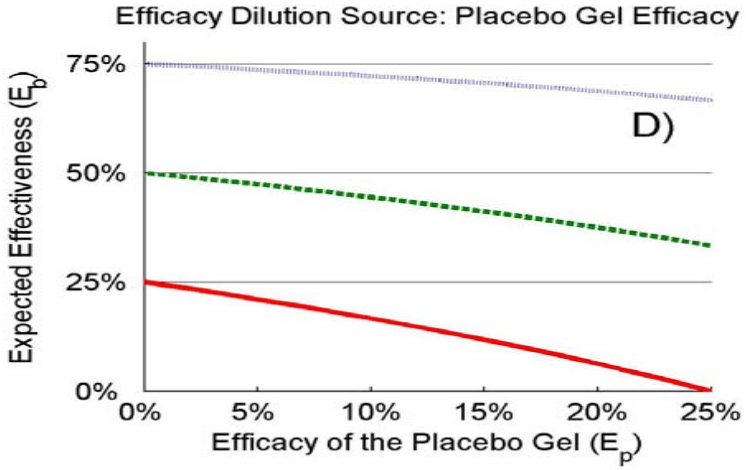
Ref: Weiss et al, *Emerg Themes Epidemiol. 2008 Jul 11;5:8*

Dilution of Efficacy from Different Sources









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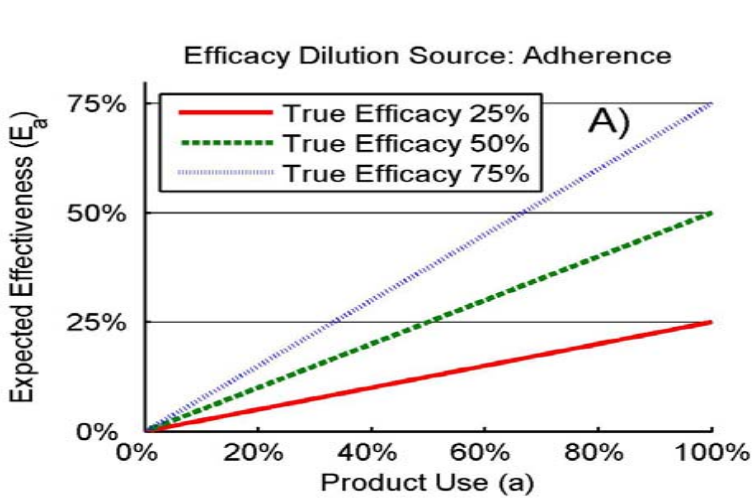

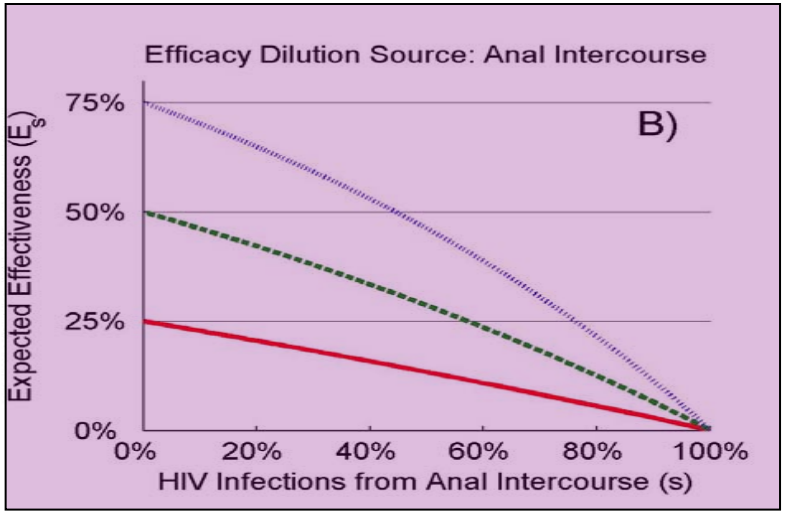

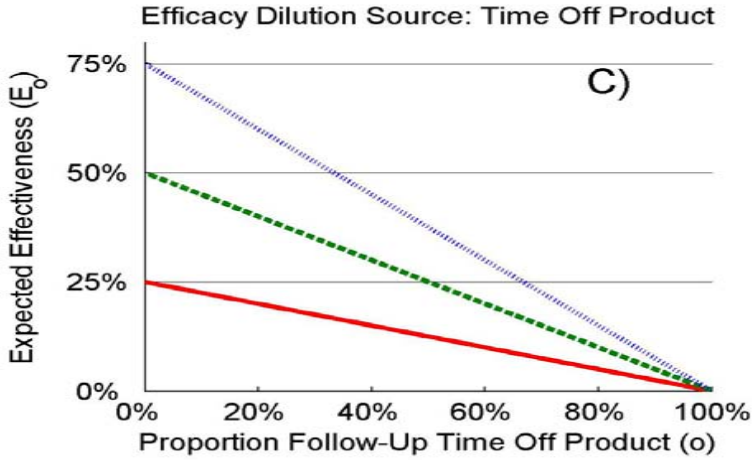

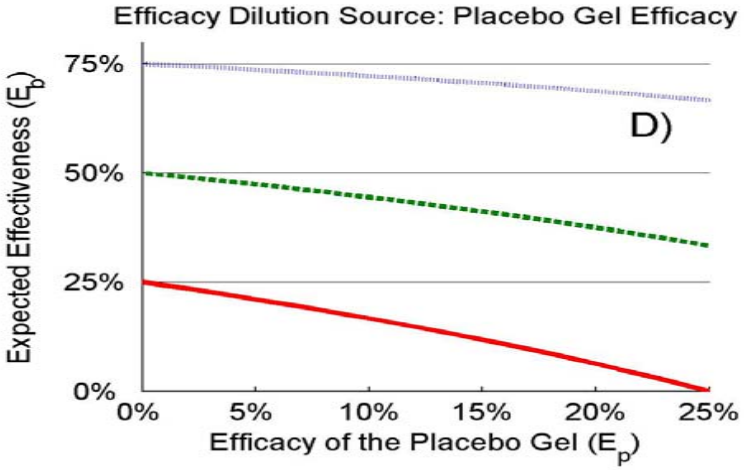

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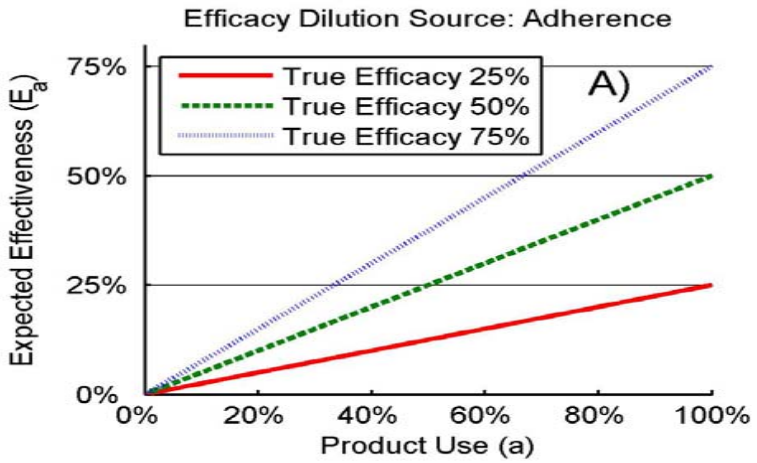

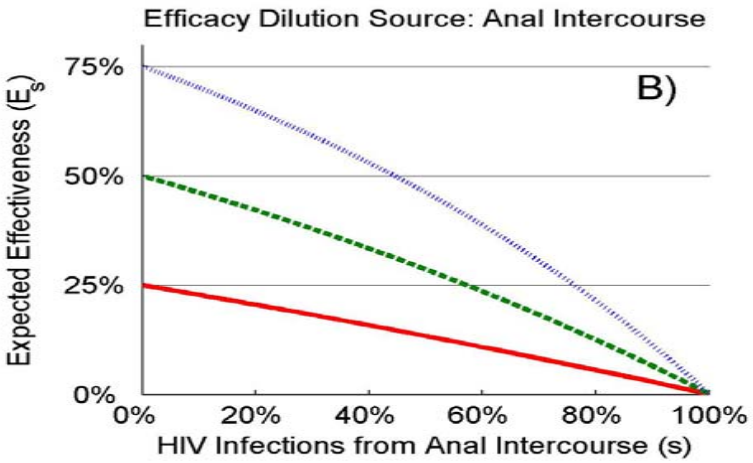

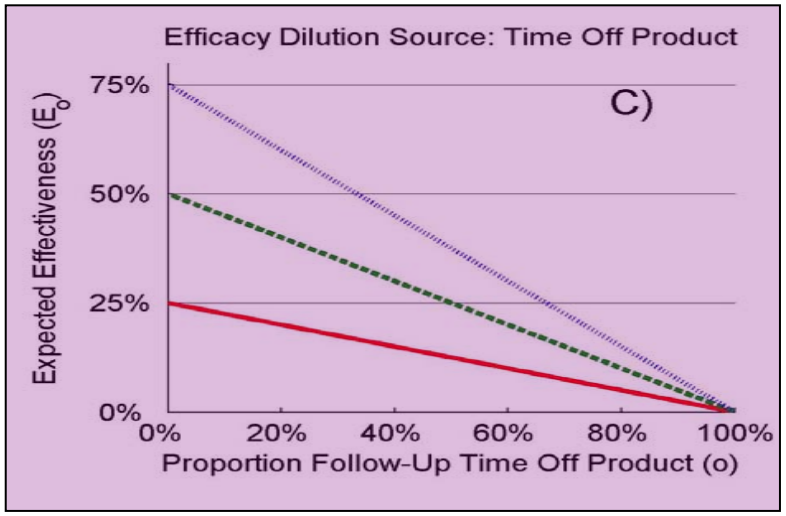

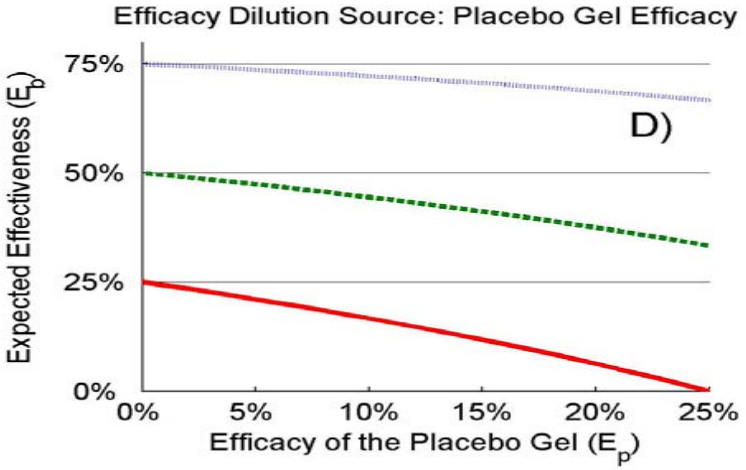

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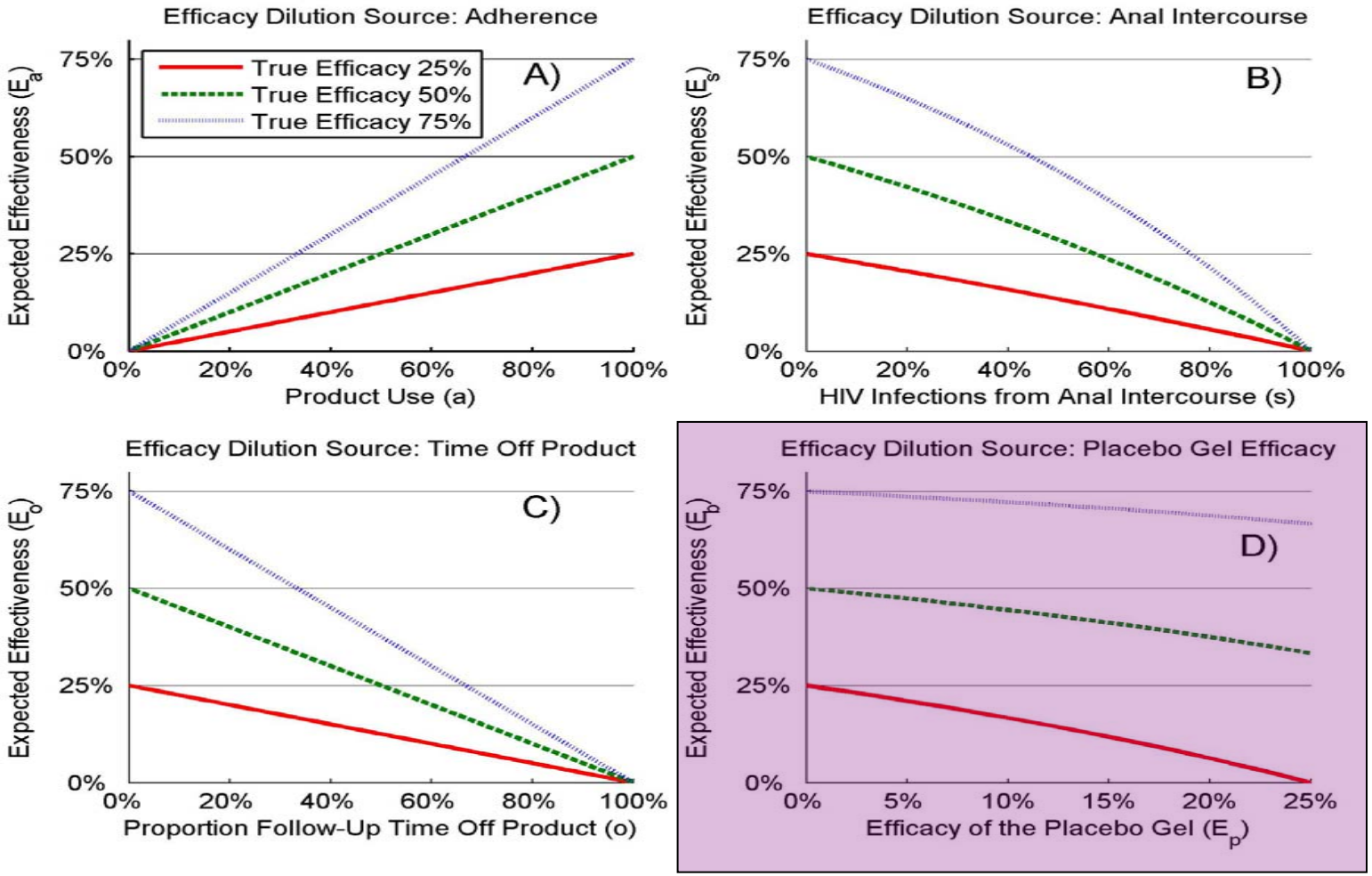


Question:

What is the level of dilution when all sources of potential dilution are present in a trial?

- Typical microbicide trials have several sources of dilution ... not just one (ie adherence)

Look at Four Scenarios:

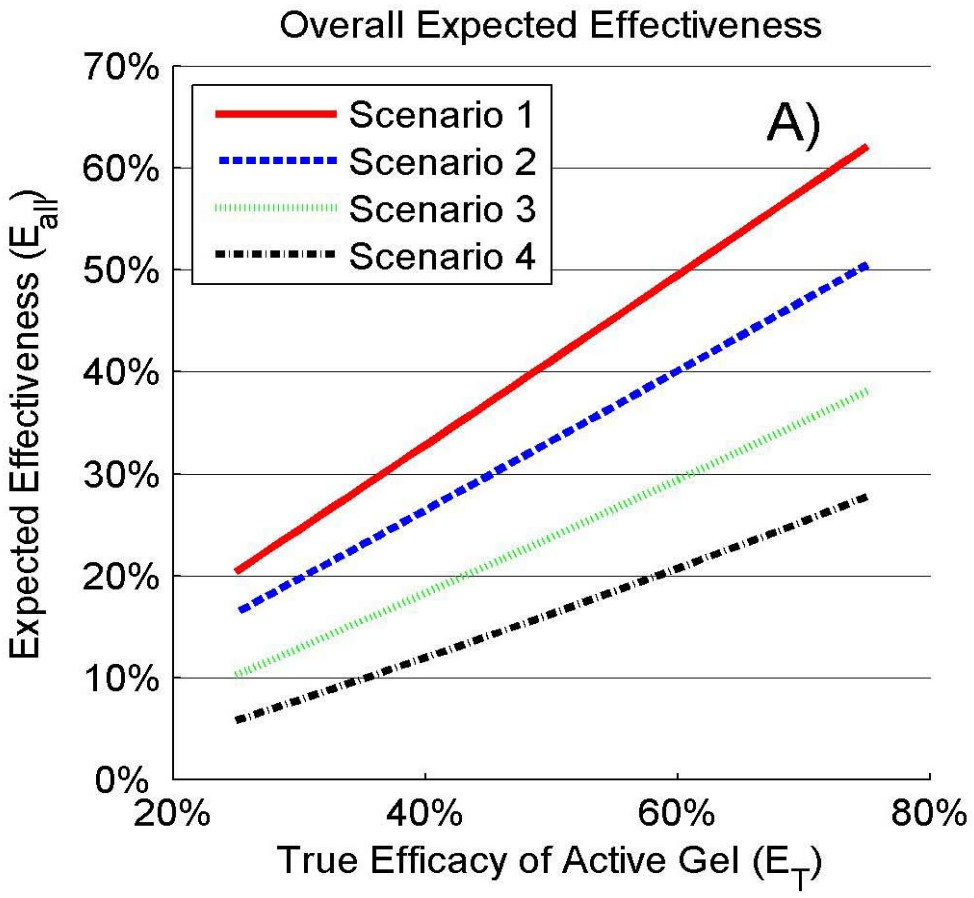
Scenario 1: Ideal trial (most likely unrealistic)

Scenario 2 & 3: More typical of what we have observed in first wave of microbicide trials

Scenario 4: Slightly more extreme but not unrealistic

	Scenario			
Source of Dilution	**1**	**2**	**3**	**4**
Adherence/Product Use	90%	80%	70%	60%
Time off product due to: pregnancy and/or AEs	5%	10%	15%	20%
Source of infection: Anal Intercourse	5%	10%	20%	30%
Placebo gel efficacy	0%	0%	5%	10%

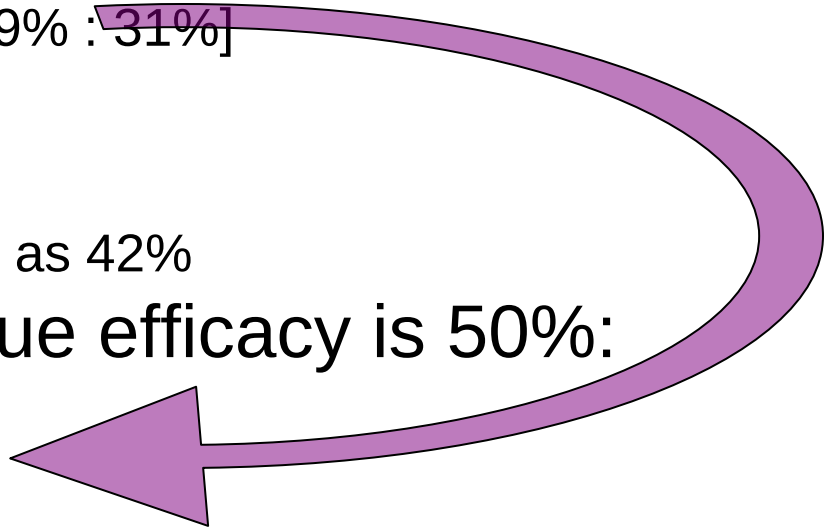
Dilution of Efficacy from All Sources: Overall Impact



	Scenario			
True Efficacy	**1**	**2**	**3**	**4**
25%	20%	16%	10%	6%
50%	41%	33%	24%	16%
75%	62%	50%	38%	28%

A Case in Point: The Carraguard Trial

- Observed effectiveness in the trial:
  - 13.0% 95% CI [-9% : 31%]
- Sources of dilution in trial
  - Non inertness of placebo gel
  - Adherence … could be as low as 42%
- Expected effectiveness if true efficacy is 50%:
  - 14.9%



Assumption:

True efficacy 50%, 20% of HIV infection from AI, 40% adherence, 10% efficacy of placebo gel, 0% time off-product due to pregnancy

Is Carraguard effective?

If Carraguard is truly effective:

- In the 40%-60% range
  - The trial had very little chance of detecting it given the potential amount of efficacy dilution in the trial
- In the range of 75%
  - In that case the overall expected effectiveness under our model would be only 25%, which remains much lower than the 33% the trial was powered to detect
    - The trial had only 51% power to detect a 25% effectiveness

Are there other sources of dilution?

- Yes !!!
  - Product is used but outside the time interval for effective use (eg within 2 hours prior to intercourse)
  - Product sharing
  - Condom use
    - a positive strong association between condom and gel use would lead to stronger dilution effects
  - Other behavioral factors associated with adherence

Conclusions

- Dilution of efficacy is potentially quite large
  - When all potential sources of dilution are taken into account
  - First generation of microbicide trials had potentially large amount of dilution
- **Important note:**

  The dilution effect will also dilute the effect of a (truly) harmful product which is increasing the risk of HIV infections. Given that a few candidate microbicides have been show to increase the risk of HIV acquisition, our results imply that these products may even be more harmful than what was observed in these trials.

Conclusions

- Use of complex statistical models
  - Need valid data on adherence and sexual behaviors (eg anal intercourse)
  - Difficult to foresee how a candidate microbicide could be marketed solely based on its favorable results on a ‘per-protocol’ analysis with non-significant ITT results

Conclusions

- Adherence
  - Optimize by counseling, counseling, & counseling
  - Develop '*valid*' measurement tools
- Source of Infections: HIV infection from anal intercourse
  - Prevent by counseling, counseling, & counseling
  - Develop '*valid*' measurement tools
- Time off-product
  - Select women with '*great care*' ie that will not become pregnant during the trial which will reduce the impact of time off-product due to pregnancy
  - Eventually, allow product use for pregnant women
- Placebo
  - Select an inert placebo gel
  - Universal placebo gel -a hydroxyethylcellulose (HEC)

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Methodology

Open Access

Efficacy dilution in randomized placebo-controlled vaginal microbicide trials

Benoit R Masse, **Marie-Claude Boily**, **Dobromir Dimitrov** and **Kamal Desai**

Emerging Themes in Epidemiology 2009, **6:**5 doi:10.1186/1742-7622-6-5

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Questions?